

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

<b>To:</b>  LANE, Graham GLAXO WELLCOME PLC Glaxo Wellcome House Berkeley Avenue Greenford Middlesex UB6 0NN GRANDE BRETAGNE	13 FEB 2001	Property NOT TC
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## PCT

### NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year)	09.02.2001
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Applicant's or agent's file reference PG3602/WO	<b>IMPORTANT NOTIFICATION</b>
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International application No. PCT/EP99/08186	International filing date (day/month/year) 01/11/1999	Priority date (day/month/year) 03/11/1998
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Applicant GLAXO GROUP LIMITED et al.
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1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
  
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
  
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

#### 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/  <div style="display: flex; align-items: center;"> <div>                     European Patent Office                      D-80298 Munich                      Tel. +49 89 2399 - 0 Tx: 523656 epmu d                      Fax: +49 89 2399 - 4465                 </div> </div>	Authorized officer  Brell, S  Tel. +49 89 2399-7271
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Form PCT/IPEA/416 (July 1992)

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## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference PG3602/WO	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP99/08186	International filing date (day/month/year) 01/11/1999	Priority date (day/month/year) 03/11/1998
International Patent Classification (IPC) or national classification and IPC C07D471/04		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  27/04/2000	Date of completion of this report  09.02.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 · Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Stellmach, J  Telephone No. +49 89 2399 8279  

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP99/08186

**I. Basis of the report**

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

**Description, pages:**

1-35 as originally filed

**Claims, No.:**

1-16 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP99/08186

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 13,14.

because:

- ☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-16

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP99/08186

No: Claims

2. Citations and explanations  
see separate sheet

**VI. Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
see separate sheet

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
see separate sheet

SECTION III -----

1. Claims 13 and 14 relate to subject-matter considered by this Authority to be covered by the provisions of **Rule 67.1(iv) PCT**. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims ( **Article 34 (4) (a) (i) PCT** ).
2. Under the terms of **Rule 39.1 (iv) PCT**, the International Preliminary Examination Authority is not required to carry out an examination of claims directed to a method of treatment of the human or animal body by surgery or therapy. As indicated in the Search Report, the search was carried out and based on the alleged effects of the compounds ( **Rule 67.1 (iv) PCT** ).

SECTION V -----

**1. Prior art**

Documents (1) - (8), which were cited in the **International Search Report** and the **Written Opinion** are considered to represent relevant prior art in this **Preliminary Examination Report**; the numbering will be adhered to in the rest of the procedure.

(1) WO-A-99/12 930

(2) WO-A-96/06 840

✓(3) WO-A-96/21 667

✓(4) WO-A-96/31 509

(5) Bioorg.Med.Chem.Lett. 7, 47 (1997)

(6) Bioorg.Med.Chem.Lett. 7, 57 (1997)

✓(7) Exp.Opin.Ther.Patents 7, 55 (1997)

(8) Exp.Opin.Ther.Patents 8, 21 (1998)

## **2. Novelty**

2.1 Document (1) is only relevant for the purposes of **Rules 33.1 c, 64.3 and 70.10 PCT** ( see also part VI, certain documents ) and since the priority document is not available are not taken into account for the Preliminary Examination Report. If the priority date is not valid for the complete claimed subject-matter, document (1) may become relevant prior art in a possible regional / national phase.

2.2 Having regard to the available prior art (2) - (8) the claimed subject-matter appears to fulfil the requirements of **Article 33 (2) PCT**, since the claimed substituted **pyrazolopyridine** derivatives differ from those of the prior art at least by the aza-bioisosteric replacement of the 6-ring hetero cycle.

## **3. Inventive step**

3.1 For the assessment of inventive step ( **Article 33 (3) PCT** ) of the claimed subject-matter, citation (2) is considered to represent the ( respective ) closest prior art. All the prior art documents (2) - (8) disclose substituted **imidazole/pyrazole diaryl** derivatives being *cyclooxygenase(COX)-inhibitors* and their structural analogues.

3.2 Starting from the ( respective ) closest prior art (2), the technical problem underlying the application in suit ( **Article 33 (3) PCT, Rule 5.1 (a) (iii) PCT** ) can be considered to be the provision of different analogues ( aza-isosteres ) with **unexpected** pharmacological ( *COX* ) activity. Since the principle of **aza-bioisosterism** is well known in the field of *cyclooxygenase(COX)-inhibitors* 'inter alia' from citations (2) - (4), the skilled person having additionally a basic knowledge of the principles of **structure-activity-relationships** would expect the claimed compounds to be to *cyclooxygenase inhibitors* i.e. the claimed derivatives must be considered as close structural analogues of some mentioned in the prior art. The skilled person having knowledge of the teaching of the prior art would thus consider some of the claimed derivatives to be *cyclooxygenase inhibitors* at least to a certain degree. For the skilled person starting from the compounds disclosed in (2), (3) or (4) there is thus a clear **incentive** that the resulting compounds are *cyclooxygenase inhibitors*, since it is known from the structural modifications performed in the citations (2) - (8) that the principle of **azabioisosterism** can be applied without essentially changing the pharmacological activity. Having regard to the structural differences as described above vis-a-vis the prior art, this modification lies within the usual skill of the application of **structure-activity-relationships**. The skilled man would have been able to predict **with certainty** that the same pharmacological activity would be retained due to these structural modifications. There is thus a rea-

sonable expectation of success to arrive at compounds being *cyclooxygenase inhibitors*. Accordingly, at present the requirements of **Article 33 (3) PCT** are not met. Given the properties to be expected for the claimed compounds ( analogues ) in comparison with those of the prior art, an **inventive step** could be recognized if the Applicant could demonstrate that the presently claimed compounds illustrate any **unpredictable** ( qualitatively or quantitatively ) pharmacological activity. The pharmacological tests performed with some of the claimed compounds ( see pages 34/35 ) cannot be taken into account, since the *cyclooxygenase inhibition* ( even *selectivity*, see citations (2) and (4) - (6) ) is not surprising.

3.3 Finally, it is realized that the Applicant is entitled to claim all obvious modifications of what he has described and that alternative variations have to be supported by a certain number of examples. Furthermore, the extent of a "reasonable generalisation" only depends upon the question of the relative distance to the prior art compounds. It is stressed that only such compounds can be claimed which are a solution to the above stated problem i.e. which illustrate the alleged unexpected pharmacological activity.

#### **4. Industrial applicability**

4.1 No objection re industrial applicability of claims 1 - 12, 15 and 16 arises insofar the claimed compounds would exhibit the alleged unexpected pharmacological properties ( **Article 33 (4) PCT** ).

4.2 For the assessment of the present claims 13 and 14 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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#### **SECTION VI -----**

#### **Certain published documents (Rule 70.10)**



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/08186

<u>Application No</u> <u>Patent No</u>	<u>Publication date</u> <u>(day/month/year)</u>	<u>Filing date</u> <u>(day/month/year)</u>	<u>Priority date (valid claim)</u> <u>(day/month/year)</u>
WO-A-99/12930	18.3.99	3.9.98	5.9.97 23.12.97

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**SECTION VII -----**

1. Since the documents (1) - (8) were not identified in the description and the relevant background art disclosed therein was not briefly discussed, the requirements of **Rule 5.1 (a) (ii) PCT** are not met.
2. The dependent claims are only possible as specific form in conjunction with independent claims of the invention ( **Rule 6.4 PCT** ).

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**SECTION VIII-----**

The Applicant is informed that the breadth of the claims has to be such that it comprises only variants which are able to solve the problem underlying the invention being a prerequisite for the acknowledgement of inventive step ( **Article 33 (3) PCT** ).

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# PCT

## REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For receiving Office use only	
International Application No.	PCT/EP 99 / 08186
International Filing Date	01 NOV 1999 (01.11.99)
EUROPEAN PATENT OFFICE PCT INTERNATIONAL APPLICATION	
Name of receiving Office and "PCT In" Application	
Applicant's or agent's file reference (if desired) (12 characters maximum)	PG3602

### Box No. I TITLE OF INVENTION

PYRAZOLOPYRIDINE DERIVATIVES

### Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Gaxo Group Limited  
Gaxo Wellcome House  
Berkeley Avenue  
Greenford, Middlesex, UB6 0NN  
GB

☐ This person is also inventor.

Telephone No. 0171 493 4060

Facsimile No. 0181 966 8838

Teleprinter No. 25456

State (i.e. country) of nationality:

GB

State (i.e. country) of residence:

GB

This person is applicant for the purposes of

☐

all designated States

☒

all designated States except the United States of America

☐

the United States of America only

☐

the States indicated in the Supplemental Box

### Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

CAMPBELL, Ian Baxter  
Gaxo Wellcome plc  
Cannels Wood Road  
Stevenage, Hertfordshire  
SG1 2NY  
GB

This person is:

☐

applicant only

☒

applicant and inventor

☐

inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

GB

State (i.e. country) of residence:

GB

This person is applicant for the purposes of

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all designated States

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all designated States except the United States of America

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the United States of America only

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the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

### Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒

agent

☐

common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country).

LANE, Graham  
Gaxo Wellcome plc  
Gaxo Wellcome House, Berkeley Avenue  
Greenford, Middlesex  
UB6 0NN  
GB

Telephone No.:

0171-493-4060

Facsimile No.:

0181-966-8838

Teleprinter No.:

25456

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

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## Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

NAYLOR, Alan  
Glaxo Wellcome plc  
Gunnels Wood Road  
Stevenage, Hertfordshire  
SG1 2NY  
GB

This person is:

- ☐ applicant only  
☒ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

GB

State (i.e. country) of residence:

GB

This person is applicant for the purposes of:

☐

all designated States

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all designated States except the United States of America

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the United States of America only

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Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only  
☐ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant for the purposes of:

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all designated States

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all designated States except the United States of America

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the United States of America only

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the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only  
☐ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

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This person is applicant for the purposes of:

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all designated States

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all designated States except the United States of America

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the United States of America only

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Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only  
☐ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant for the purposes of:

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all designated States

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all designated States except the United States of America

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☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

**Box No. V DESIGNATION OF STATES**

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

**Regional Patent**

- ☒ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line).....

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| <input checked="" type="checkbox"/> <b>GD</b> Grenada                               | <input checked="" type="checkbox"/> <b>SK</b> Slovakia                                                       |
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| <input checked="" type="checkbox"/> <b>KG</b> Kyrgyzstan                            | <input checked="" type="checkbox"/> <b>ZA</b> South Africa                                                   |
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| <input checked="" type="checkbox"/> <b>KR</b> Republic of Korea                     | <input checked="" type="checkbox"/> <b>CR</b> Costa Rica                                                     |
| <input checked="" type="checkbox"/> <b>KZ</b> Kazakhstan                            |                                                                                                              |
| <input checked="" type="checkbox"/> <b>LC</b> Saint Lucia                           | <input checked="" type="checkbox"/> <b>DM</b> Dominica                                                       |
| <input checked="" type="checkbox"/> <b>LK</b> Sri Lanka                             | <input checked="" type="checkbox"/> <b>MA</b> Morocco                                                        |
|                                                                                     | <input checked="" type="checkbox"/> <b>TZ</b> Tanzania                                                       |

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

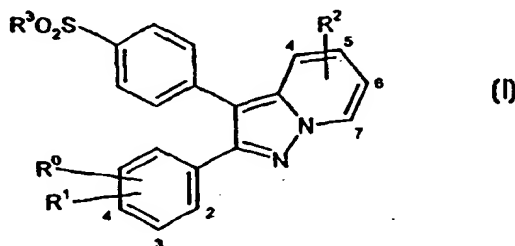
Date of receipt of the record copy by the International Bureau \_\_\_\_\_



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : C07D 471/04, A61K 31/435 // (C07D 471/04, 231:00, 221:00)		A1	(11) International Publication Number: WO 00/26216
			(43) International Publication Date: 11 May 2000 (11.05.00)
(21) International Application Number: PCT/EP99/08186		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 1 November 1999 (01.11.99)		<p>Published</p> <p><i>With international search report.</i></p> <p><i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
(30) Priority Data:			
9824062.5 3 November 1998 (03.11.98) GB			
9920909.0 3 September 1999 (03.09.99) GB			
(71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): CAMPBELL, Ian, Baxter [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). NAYLOR, Alan [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).			
(74) Agent: LANE, Graham; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).			

(54) Title: PYRAZOLOPYRIDINE DERIVATIVES AS SELECTIVE COX-2 INHIBITORS



## (57) Abstract

The invention provides the compounds of formula (I) and pharmaceutically acceptable derivatives thereof in which :  $R^0$  and  $R^1$  are independently selected from H, halogen,  $C_1$ -alkyl,  $C_1$ -alkoxy, or  $C_1$ -alkoxy substituted by one or more fluorine atoms;  $R^2$  is H,  $C_1$ -alkyl,  $C_1$ -alkyl substituted by one or more fluorine atoms,  $C_1$ -alkoxy,  $C_1$ -hydroxyalkyl,  $SC_1$ -alkyl,  $C(O)H$ ,  $C(O)C_1$ -alkyl,  $C_1$ -alkylsulphonyl,  $C_1$ -alkoxy substituted by one or more fluorine atoms; and  $R^3$  is  $C_1$ -alkyl or  $NH_2$ . Compounds of formula (I) are potent and selective inhibitors of COX-2 and are of use in the treatment of the pain, fever, inflammation of a variety of conditions and diseases.

From the INTERNATIONAL SEARCHING AUTHORITY


PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT  
OR THE DECLARATION

(PCT Rule 44.1)

To: GLAXO WELLCOME PLC Glaxo Wellcome House Attn. Lane, Graham Berkeley Avenue Greenford Middlesex UB6 0NN UNITED KINGDOM		Intellectual Property - 1 MAR 2000 INIT CW FILE TC
Applicant's or agent's file reference PG3602		Date of mailing (day/month/year) 28/02/2000 ✓
International application No. PCT/EP 99/08186		FOR FURTHER ACTION See paragraphs 1 and 4 below International filing date (day/month/year) 01/11/1999
Applicant GLAXO GROUP LIMITED et al.		

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.  
Filing of amendments and statement under Article 19:  
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):  
When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.  
Where? Directly to the International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Facsimile No.: (41-22) 740.14.35  
For more detailed instructions, see the notes on the accompanying sheet.
2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:  
☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.  
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.
4. Further action(s): The applicant is reminded of the following:  
Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.  
Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).  
Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Véronique Baillou
-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

## INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

### What documents must/may accompany the amendments?

#### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.



## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

**It must be in the language in which the international application is to be published.**

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>PG3602</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/EP 99/ 08186</b>	International filing date (day/month/year) <b>01/11/1999</b>	(Earliest) Priority Date (day/month/year) <b>03/11/1998</b>
Applicant <b>GLAXO GROUP LIMITED et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.  
☒ It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

## 4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**PYRAZOLOPYRIDINE DERIVATIVES AS SELECTIVE COX-2 INHIBITORS**

## 5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

## 6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No.

/EP 99/08186

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04 A61K31/435 //(C07D471/04,231:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 12930 A (NAYLOR ALAN ;BESWICK PAUL (GB); CAMPBELL IAN (GB); GLAXO GROUP LTD) 18 March 1999 (1999-03-18) the whole document	1-16
Y	WO 96 06840 A (MERCK FROSST CANADA INC ;PRASIT PETPIBOON (CA); GUAY DANIEL (CA);) 7 March 1996 (1996-03-07) * see exs. 4 and 5 and last 3 exs. on page 31 * the whole document	1-16
Y	WO 96 31509 A (GLAXO GROUP LTD ;BESWICK PAUL JOHN (GB); CAMPBELL IAN BAXTER (GB);) 10 October 1996 (1996-10-10) the whole document	1-16

-/-

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

18 February 2000

Date of mailing of the international search report

28/02/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl;  
Fax: (+31-70) 340-3016

Authorized officer

Stellmach, J

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 21667 A (MERCK FROSST CANADA INC ;GAUTHIER JACQUES YVES (CA); LAU CHEUK K ( ) 18 July 1996 (1996-07-18) the whole document	1-16
Y	<p> THERIEN M ET AL: "Synthesis and  biological evaluation of  5,6-diarylimidazo'2.1-b!thiaz ole as  selective COX-2 inhibitors"  BIOORGANIC &amp; MEDICINAL CHEMISTRY  LETTERS,GB,OXFORD,  vol. 7, no. 1,  7 January 1997 (1997-01-07), pages 47-52,  XP004135964  ISSN: 0960-894X  the whole document </p>	1-16
Y	<p> ROY P ET AL: "A new series of selective  COX-2 inhibitors:  5,6-diarylthiazolo'3,2-b!  '1,2,4!triazoles"  BIOORGANIC &amp; MEDICINAL CHEMISTRY  LETTERS,GB,OXFORD,  vol. 7, no. 1,  7 January 1997 (1997-01-07), pages 57-62,  XP004135966  ISSN: 0960-894X  the whole document </p>	1-16
Y	<p> TALLEY J J: "Selective inhibitors of  cyclooxygenase-2"  EXPERT OPINION ON THERAPEUTIC  PATENTS,GB,ASHLEY PUBLICATIONS,  vol. 7, no. 1,  1 January 1997 (1997-01-01), pages 55-62,  XP002086250  ISSN: 1354-3776  * see page 59, cpds. 13-15 *  the whole document </p>	1-16
Y	<p> CARTER J S: "Recently reported inhibitors  of cyclooxygenase-2"  EXPERT OPINION ON THERAPEUTIC  PATENTS,GB,ASHLEY PUBLICATIONS,  vol. 8, no. 1,  1 January 1998 (1998-01-01), pages 21-29,  XP002086251  ISSN: 1354-3776  the whole document </p>	1-16

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

CT/EP 99/08186

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
W0 9912930	A	18-03-1999	AU	9439598 A	29-03-1999
W0 9606840	A	07-03-1996	US	5521213 A	28-05-1996
			AU	689302 B	26-03-1998
			AU	3249295 A	22-03-1996
			CA	2197895 A	07-03-1996
			EP	0778834 A	18-06-1997
			JP	10504829 T	12-05-1998
W0 9631509	A	10-10-1996	AU	5276696 A	23-10-1996
			BG	101934 A	30-04-1999
			BR	9604870 A	26-05-1998
			CA	2216809 A	10-10-1996
			CN	1186492 A	01-07-1998
			CZ	9703133 A	18-03-1998
			EP	0819127 A	21-01-1998
			HU	9801602 A	30-11-1998
			JP	11501049 T	26-01-1999
			NO	974595 A	03-12-1997
			NZ	304886 A	25-11-1998
			PL	322623 A	02-02-1998
			SK	133297 A	08-07-1998
W0 9621667	A	18-07-1996	US	5552422 A	03-09-1996
			AU	697650 B	15-10-1998
			AU	4381496 A	31-07-1996
			CA	2209895 A	18-07-1996
			EP	0802917 A	29-10-1997
			JP	11501902 T	16-02-1999

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PG3602/WO	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP99/08186	International filing date (day/month/year) 01/11/1999	Priority date (day/month/year) 03/11/1998
International Patent Classification (IPC) or national classification and IPC C07D471/04		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 8 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  27/04/2000	Date of completion of this report  09.02.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Stellmach, J  Telephone No. +49 89 2399 8279



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/08186

## I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

**Description, pages:**

1-35 as originally filed

**Claims, No.:**

1-16 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/08186

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 13,14.

because:

☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	

Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16

Industrial applicability (IA)	Yes:	Claims	1-16
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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP99/08186

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No:      Claims

2. Citations and explanations  
**see separate sheet**

**VI.      Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

SECTION III -----

1. Claims 13 and 14 relate to subject-matter considered by this Authority to be covered by the provisions of **Rule 67.1(iv) PCT**. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims ( **Article 34 (4) (a) (i) PCT** ).
2. Under the terms of **Rule 39.1 (iv) PCT**, the International Preliminary Examination Authority is not required to carry out an examination of claims directed to a method of treatment of the human or animal body by surgery or therapy. As indicated in the Search Report, the search was carried out and based on the alleged effects of the compounds ( **Rule 67.1 (iv) PCT** ).

SECTION V -----

**1. Prior art**

Documents (1) - (8), which were cited in the **International Search Report** and the **Written Opinion** are considered to represent relevant prior art in this **Preliminary Examination Report**; the numbering will be adhered to in the rest of the procedure.

- (1) WO-A-99/12 930
- (2) WO-A-96/06 840
- (3) WO-A-96/21 667
- (4) WO-A-96/31 509
- (5) Bioorg.Med.Chem.Lett. 7, 47 (1997)
- (6) Bioorg.Med.Chem.Lett. 7, 57 (1997)
- (7) Exp.Opin.Ther.Patents 7, 55 (1997)
- (8) Exp.Opin.Ther.Patents 8, 21 (1998)

## 2. Novelty

2.1 Document (1) is only relevant for the purposes of **Rules 33.1 c, 64.3 and 70.10 PCT** ( see also part VI, certain documents ) and since the priority document is not available are not taken into account for the Preliminary Examination Report. If the priority date is not valid for the complete claimed subject-matter, document (1) may become relevant prior art in a possible regional / national phase.

2.2 Having regard to the available prior art (2) - (8) the claimed subject-matter appears to fulfil the requirements of **Article 33 (2) PCT**, since the claimed substituted **pyrazolopyridine** derivatives differ from those of the prior art at least by the aza-bioisosteric replacement of the 6-ring hetero cycle.

## 3. Inventive step

3.1 For the assessment of inventive step ( **Article 33 (3) PCT** ) of the claimed subject-matter, citation (2) is considered to represent the ( respective ) closest prior art. All the prior art documents (2) - (8) disclose substituted **imidazole/pyrazole diaryl** derivatives being *cyclooxygenase(COX)-inhibitors* and their structural analogues.

3.2 Starting from the ( respective ) closest prior art (2), the technical problem underlying the application in suit ( **Article 33 (3) PCT, Rule 5.1 (a) (iii) PCT** ) can be considered to be the provision of different analogues ( aza-isosteres ) with **unexpected** pharmacological ( *COX* ) activity. Since the principle of **aza-bioisosterism** is well known in the field of *cyclooxygenase(COX)-inhibitors* 'inter alia' from citations (2) - (4), the skilled person having additionally a basic knowledge of the principles of **structure-activity-relationships** would expect the claimed compounds to be to *cyclooxygenase inhibitors* i.e. the claimed derivatives must be considered as close structural analogues of some mentioned in the prior art. The skilled person having knowledge of the teaching of the prior art would thus consider some of the claimed derivatives to be *cyclooxygenase inhibitors* at least to a certain degree. For the skilled person starting from the compounds disclosed in (2), (3) or (4) there is thus a clear **incentive** that the resulting compounds are *cyclooxygenase inhibitors*, since it is known from the structural modifications performed in the citations (2) - (8) that the principle of **azabioisosterism** can be applied without essentially changing the pharmacological activity. Having regard to the structural differences as described above vis-a-vis the prior art, this modification lies within the usual skill of the application of **structure-activity-relationships**. The skilled man would have been able to predict **with certainty** that the same pharmacological activity would be retained due to these structural modifications. There is thus a rea-

sonable expectation of success to arrive at compounds being *cyclooxygenase inhibitors*. Accordingly, at present the requirements of **Article 33 (3) PCT** are not met. Given the properties to be expected for the claimed compounds ( analogues ) in comparison with those of the prior art, an **inventive step** could be recognized if the Applicant could demonstrate that the presently claimed compounds illustrate any **unpredictable** ( qualitatively or quantitatively ) pharmacological activity. The pharmacological tests performed with some of the claimed compounds ( see pages 34/35 ) cannot be taken into account, since the *cyclooxygenase inhibition* ( even *selectivity*, see citations (2) and (4) - (6) ) is not surprising.

3.3 Finally, it is realized that the Applicant is entitled to claim all obvious modifications of what he has described and that alternative variations have to be supported by a certain number of examples. Furthermore, the extent of a "reasonable generalisation" only depends upon the question of the relative distance to the prior art compounds. It is stressed that only such compounds can be claimed which are a solution to the above stated problem i.e. which illustrate the alleged unexpected pharmacological activity.

#### **4. Industrial applicability**

4.1 No objection re industrial applicability of claims 1 - 12, 15 and 16 arises insofar the claimed compounds would exhibit the alleged unexpected pharmacological properties ( **Article 33 (4) PCT** ).

4.2 For the assessment of the present claims 13 and 14 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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#### SECTION VI -----

#### **Certain published documents (Rule 70.10)**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/08186

<u>Application No</u> <u>Patent No</u>	<u>Publication date</u> <u>(day/month/year)</u>	<u>Filing date</u> <u>(day/month/year)</u>	<u>Priority date (valid claim)</u> <u>(day/month/year)</u>
WO-A-99/12930	18.3.99	3.9.98	5.9.97 23.12.97

\*\*\*\*\*

**SECTION VII -----**

1. Since the documents (1) - (8) were not identified in the description and the relevant background art disclosed therein was not briefly discussed, the requirements of **Rule 5.1 (a) (ii) PCT** are not met.
2. The dependent claims are only possible as specific form in conjunction with independent claims of the invention ( **Rule 6.4 PCT** ).

\*\*\*\*\*

**SECTION VIII-----**

The Applicant is informed that the breadth of the claims has to be such that it comprises only variants which are able to solve the problem underlying the invention being a prerequisite for the acknowledgement of inventive step ( **Article 33 (3) PCT** ).

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# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>PG3602</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. <b>PCT/EP 99/ 08186</b>	International filing date (day/month/year) <b>01/11/1999</b>	(Earliest) Priority Date (day/month/year) <b>03/11/1998</b>
Applicant  <b>GLAXO GROUP LIMITED et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

### 1. Basis of the report

a. With regard to the language, the International search was carried out on the basis of the International application in the language in which it was filed, unless otherwise indicated under this item.

☐ the International search was carried out on the basis of a translation of the International application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the International application, the International search was carried out on the basis of the sequence listing:

☐ contained in the International application in written form.

☐ filed together with the International application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the International application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

### 4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**PYRAZOLOPYRIDINE DERIVATIVES AS SELECTIVE COX-2 INHIBITORS**

### 5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International search report, submit comments to this Authority.

### 6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

**PCT/EP 99/08186**

IPC 7 C07D471/04 A61K31/435 //(C07D471/04,231:00,221:00)

## Stellmach, J

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 99/08186

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 21667 A (MERCK FROSST CANADA INC ;GAUTHIER JACQUES YVES (CA); LAU CHEUK K ( ) 18 July 1996 (1996-07-18) the whole document ---	1-16
Y	THERIEN M ET AL: "Synthesis and biological evaluation of 5,6-diarylimidazo'2.1-b'thiaz ole as selective COX-2 inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 7, no. 1, 7 January 1997 (1997-01-07), pages 47-52, XP004135964 ISSN: 0960-894X the whole document ---	1-16
Y	ROY P ET AL: "A new series of selective COX-2 inhibitors: 5,6-diarylthiazolo'3,2-b! '1,2,4!triazoles" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 7, no. 1, 7 January 1997 (1997-01-07), pages 57-62, XP004135966 ISSN: 0960-894X the whole document ---	1-16
Y	TALLEY J J: "Selective inhibitors of cyclooxygenase-2" EXPERT OPINION ON THERAPEUTIC PATENTS,GB,ASHLEY PUBLICATIONS, vol. 7, no. 1, 1 January 1997 (1997-01-01), pages 55-62, XP002086250 ISSN: 1354-3776 * see page 59, cpds. 13-15 * the whole document ---	1-16
Y	CARTER J S: "Recently reported inhibitors of cyclooxygenase-2" EXPERT OPINION ON THERAPEUTIC PATENTS,GB,ASHLEY PUBLICATIONS, vol. 8, no. 1, 1 January 1998 (1998-01-01), pages 21-29, XP002086251 ISSN: 1354-3776 the whole document -----	1-16



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/08186

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9912930	A	18-03-1999	AU	9439598 A	29-03-1999
WO 9606840	A	07-03-1996	US	5521213 A	28-05-1996
			AU	689302 B	26-03-1998
			AU	3249295 A	22-03-1996
			CA	2197895 A	07-03-1996
			EP	0778834 A	18-06-1997
			JP	10504829 T	12-05-1998
WO 9631509	A	10-10-1996	AU	5276696 A	23-10-1996
			BG	101934 A	30-04-1999
			BR	9604870 A	26-05-1998
			CA	2216809 A	10-10-1996
			CN	1186492 A	01-07-1998
			CZ	9703133 A	18-03-1998
			EP	0819127 A	21-01-1998
			HU	9801602 A	30-11-1998
			JP	11501049 T	26-01-1999
			NO	974595 A	03-12-1997
			NZ	304886 A	25-11-1998
			PL	322623 A	02-02-1998
			SK	133297 A	08-07-1998
WO 9621667	A	18-07-1996	US	5552422 A	03-09-1996
			AU	697650 B	15-10-1998
			AU	4381496 A	31-07-1996
			CA	2209895 A	18-07-1996
			EP	0802917 A	29-10-1997
			JP	11501902 T	16-02-1999